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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/751,826

01/05/2004

Cecile Casterman

A0848.70021US08

4193

23628 7590 11/18/2009
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EXAMINER

DIBRINO, MARIANNE NMN

ART UNIT

PAPER NUMBER

1644

MAIL DATE

DELIVERY MODE

11/18/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/751,826	Applicant(s) CASTERMAN ET AL.	
	Examiner MARIANNE DIBRINO	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 June 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18, 19, 22-36, 51-56, 59 and 64-69 is/are pending in the application.
- 4a) Of the above claim(s) 23, 24, 29 and 64-69 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 18 and 25 is/are allowed.
- 6) ☒ Claim(s) 19, 22, 26-28, 30-36, 51-56 and 59 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/7/09, 6/23/09, 3/26/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendment and response filed 6/23/09 is acknowledged and has been entered.
2. Applicant is reminded of Applicant's election of Group I and species of fragment of an immunoglobulin which is the variable region of a heavy chain, said variable region devoid of normal light chain interaction sites, and Applicant's election with traverse of the species of "labeled with a detectable label" that is "a radioactive label" in Applicant's response filed 1/23/06.

Claims 18, 19, 22, 25-27, 31-33, 35 and 51-54 read upon the elected species.

Applicant is reminded that upon consideration of the prior art, the search had been extended to include the species recited in instant claim 22, *i.e.*, "or a fragment thereof according to claim 19, which has a constant region which is devoid of a CH1 domain."

Applicant is reminded that upon consideration of prior art document EP 0584421 A1, examination has been extended to include the species of VHH recited in instant claims 28, 30, 34, 36, 55, 56 and 59.

Claims 18, 19, 22, 25-28, 30-36, 51-56 and 59 are presently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 51-56 and 59 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the disclosure as originally filed is as follows: a variable region of a heavy polypeptide chain and a fragment of a variable region.

Applicant had previously deleted the limitation "of an immunoglobulin" from the instant claims, creating more than one new genus.

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5. Claims 19, 22, 26-28 and 30-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

This ground of rejection is necessitated by Applicant's amendment filed 6/23/09.

The amendatory material not supported by the disclosure as originally filed is as follows: a fragment of a variable region of a heavy polypeptide chain of an immunoglobulin.

Applicant points to support for a fragment of a variable region of a heavy polypeptide chain [of an immunoglobulin] in the specification on page 15 at lines 22-26; however, the support in the originally filed disclosure at the cited location is "a fragment of at least 10 preferably 20 amino acids of the variable region of the immunoglobulin, or the complete variable region".

Applicant has thus claimed a genus of fragments of a variable region of a heavy polypeptide chain of an immunoglobulin that includes fragments of an immunoglobulin that are less than 10 amino acid residues, and those fragments that are less than 10 amino acid residues are not supported by the originally filed disclosure.

6. For the purpose of prior art rejections, the filing date of instant claims 19, 22, 26-28, 30-36, 51-56 and 59 is deemed to be the filing date of the instant application, *i.e.*, 1/5/04, as the parent applications do not support the claimed limitation of the instant claims as enunciated at item #4 and #5 *supra* of this Office Action. In addition, with regard to the instant claims that recite a fragment of a variable region of a heavy polypeptide chain of an immunoglobulin, the foreign priority documents do not support the said limitation. EP 0584421 A1 which is the publication of EP application 92402326.0, one of Applicant's foreign priority documents, discloses fragments of variable region of heavy chain antibodies that are specific lengths only, including those at least 10 amino acid residues in length.

7. Applicant's amendment filed 6/23/09 has overcome the prior rejection of record of claims 22 and 27 under 35 U.S.C. 102(b) as being anticipated by Ungar-Waron *et al* (Isr. J. Vet. Med. 1987, Vol. 43(3), pages 198-203, IDS reference) as evidenced by Hamers-Casterman *et al* (Nature 3 June 1993, Vol. 363, pages 446-448, IDS reference), Roux *et al* (PNAS USA 1998, Vol. 95, pages 11804-11809, IDS reference), WO 94/25591 (Applicant's IDS reference in the Form-1449 filed 7/24/06), and van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record).

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8. Applicant's amendment filed 6/23/09 has overcome the prior rejection of record of claims 22 and 27 under 35 U.S.C. 102(b) as being anticipated by Grover *et al* (Ind. J. Biochem. Biophys. 1983, 20(4): 238-240, IDS reference filed 7/24/06, of record) as evidenced by WO 94/25591 (IDS reference filed 7/24/06) and van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record).

9. Applicant's amendment filed 6/23/09 has overcome the prior rejection of record of claims 18, 22, 25 and 27 under 35 U.S.C. 102(b) as being anticipated by Frenken *et al* (J. of Biotechnology, 2000, 78: 11-21, of record).

10. Claims 19, 26, 31-33, 35, 51-53, 55 and 59 stand rejected under 35 U.S.C. 102(b) as being anticipated by Frenken *et al* (J. of Biotechnology, 2000, 78: 11-21, of record).

Frenken *et al* teach VHH fragments of Camelid antibodies specific for a hapten (*i.e.*, the variable region of a heavy chain antibody devoid of light chains), and that these fragments may be produced in a eukaryotic host cell such as the yeast *S. cerevisiae*, these fragments labeled with an enzymatic marker or with a chemical marker or with a c-myc tag (see entire reference, especially abstract, introduction, sections 2.2 and 3.3 and discussion). Frenken *et al* teach a fragment of one of the VHHs that binds antigen (Section 3.3).

Claims 31 and 32 are included in this rejection because the intended uses of the product "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis," respectively, do not carry patentable weight per se.

Claims 51-53 are included in this rejection because the art reference teaches samples of culture media containing secreted VHH fragments, *i.e.*, a "composition".

Claim 59 is included in this rejection because it is an inherent property of the VHH that it is capable of targeting drugs, hormones or cytokines to cells.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the amendment filed 6/23/09 on pages 9-10.

Applicant argues that Frenken *et al* was published after the priority date of the instant application.

However, the instant claims have the priority date of the instant application as enunciated supra, and hence Frenken *et al* is available as prior art.

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11. Applicant's amendment filed 6/23/09 has overcome the prior rejection of record of claims 18, 22, 25, 27 and 52 under 35 U.S.C. 102(b) as being anticipated by Lauwereys *et al* (The EMBO Journal, 1998, 17(13): 3512-3520, of record).

12. Claims 19, 31-35, 51, 53, 55 and 59 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lauwereys *et al* (The EMBO Journal, 1998, 17(13): 3512-3520, of record).

Lauwereys *et al* teach single chain *Camelid* antibodies, devoid of normal light chain interaction sites, as well as variable domain fragments (VHH) of said antibodies, including wherein the fragments are labeled with a chemical marker (on SDS-PAGE) or with an enzymatic marker (in ELISA), or monomeric heavy chains of the Camelid IgG2 and IgG3 antibodies that are devoid of light chains, including labeled with a chemical marker (on SDS-PAGE) (see entire reference). Lauwereys *et al* teach fragments of the VHH fragments such as CDRs or frameworks.

Claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claim 51 is included in this rejection because the art reference teaches phage display and also liquid compositions comprising a *Camelid* VHH single domain fragment *i.e.*, a "composition comprising a variable region of a heavy polypeptide chain...".

Claim 59 is included in this rejection because it is an inherent property of the VHH that it is capable of targeting drugs, hormones or cytokines to cells.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the amendment filed 6/23/09 on page 10.

Applicant argues that Lauwereys *et al* was published after the priority date of the instant application.

However, the instant claims have the priority date of the instant application as enunciated *supra*, and hence Lauwereys *et al* is available as prior art.

13. Applicant's amendment filed 6/23/09 has overcome the prior rejection of record of claims 18 and 25 under 35 U.S.C. 102(b) as being anticipated by EP 0584421 A1.

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14. Claims 19, 22, 26-28, 30-36, 51-56 and 59 stand rejected under 35 U.S.C. 102(b) as being anticipated by EP 0584421 A1 (3/2/94, of record).

EP 0584421 A1 teaches VHH fragments of heavy chain antibodies from *Camelids* as well as fragments of the variable region of the *Camelid* antibodies that are at least 10 or at least 20 amino acids in length. EP 0584421 A1 also teaches the entire heavy chain antibody that comprises a constant region devoid of the CH1 domain (especially claim 16). EP 0584421 A1 teaches the antibodies or fragments thereof against proteins, haptens, carbohydrates or nucleic acids, or labeled with a detectable label such as an enzymatic marker, a radioactive marker, technetium (an imaging agent), a chemiluminescent marker, a drug, a hormone, a cytokine, or a toxin such as mistletoe lectin toxin, the constructs being capable of targeting the added toxin, drug, hormone or cytokine. EP 0584421 A1 teaches a modified four chain immunoglobulin or fragment thereof in which the VH regions have been partially replaced by specific sequences or amino acid residues of VHH (especially page 10, page 11 at the first thirty lines). EP 0584421 A1 teaches a fragment of a variable region which comprises at least 10 amino acid residues of the VHH and comprises a charged amino acid residue or cysteine at position 45 (especially page 5 at lines 24-37, claim 16). EP 0584421 A1 teaches that the specificity of the VHH can be anti-idiotypic (especially page 6).

Claims 31 and 32 are included in this rejection because the intended uses of the immunoglobulin “suitable for use in *in vitro* diagnosis” or “suitable for use in *in vivo* diagnosis”, respectively, do not carry patentable weight per se.

Claims 22 and 27 are included in this rejection because EP 0584421 A1 teaches the variable region fused to all or part of the constant region of a human antibody (especially page 5 at lines 47-51).

Applicant's said arguments are of record in the amendment filed 6/23/09 on page 10.

Applicant argues that EP 0584421 A1 was published after the priority date of the instant application.

However, the instant claims have the priority date of the instant application as enunciated supra, and hence EP 0584421 A1 is available as prior art.

15. Applicant's amendment filed 6/23/09 has overcome the prior rejection of record of claims 18, 22, 25 and 27 under 35 U.S.C. 102(b) as being anticipated by Cortex-Retamozo *et al* (Int. J. Cancer, 2002, 98: 456-462, of record).

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16. Claims 30-35, 51, 53, 54 and 59 stand rejected under 35 U.S.C. 102(b) as being anticipated by Cortex-Retamozo *et al* (Int. J. Cancer, 2002, 98: 456-462, of record).

Cortex-Retamozo *et al* teach a VHH antibody, or a bivalent construct thereof, and including labeled with a radioactive label, and that the specificity of the VHH antibody fragment is directed against a transfected protein present on the surface of a tumor cell (see entire reference).

Claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claim 30 is included in this rejection because Cortex-Retamozo *et al* also teach camelization of human antibody fragments (see reference 24 on page 462).

Claim 59 is included in this rejection because it is an inherent property of the VHH antibody that it is capable of targeting drugs, hormones or cytokines to cells.

Applicant's said arguments are of record in the amendment filed 6/23/09 on page 11.

Applicant argues that EP 0584421 A1 was published after the priority date of the instant application.

However, the instant claims have the priority date of the instant application as enunciated supra, and hence EP 0584421 A1 is available as prior art.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. Claims 19, 26, 33-35, 51-55 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Frenken *et al* (J. of Biotechnology, 2000, 78: 11-21, of record) or EP 0584421 A1 (of record) in view of Power and Hudson (Expert Opin. Biol. Ther. 2003, 3(2): 385-389, of record).

(Claims 26, 55 and 59 are presently anticipated by the Frenken *et al* reference, and so are also listed in this obviousness rejection.)

The primary references Frenken *et al* or EP 0584421 A1 have both been discussed supra.

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These primary references do not teach wherein the variable region or the fragment thereof specifically binds a protein present on tumor cells (as recited in instant claim 54).

Power and Hudson teach proteins on the surface of tumor cells that are targets for antibody therapy (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art to generate a VHH antibody or fragment thereof such as taught by Frenken *et al* or by EP 0584421 A1 having specificity for a tumor target protein such as taught by Power and Hudson, and to have included them in a composition.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a composition for tumor therapy.

Furthermore, Power and Hudson teach designing these antibodies with radionuclides, toxins, enzymes, and drugs for clinical diagnosis and therapy (especially abstract and conclusion).

It would have been prima facie obvious to one of ordinary skill in the art to make an immunoconjugate such as taught by Power and Hudson using the antibody composition of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a composition for diagnosis and therapy.

19. Claims 19, 31-35, 51, 53-55 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lauwereys *et al* (The EMBO Journal, 1998, 17(13): 3512-3520, of record) in view of Power and Hudson (Expert Opin. Biol. Ther. 2003, 3(2): 385-389).

(Claims 19, 31-35, 51, 53, 55 and 59 are presently anticipated by the Lauwereys *et al* reference, and so are also listed in this obviousness rejection.)

The primary reference Lauwereys *et al* has been discussed supra.

The primary reference does not teach wherein the variable region specifically binds a protein present on tumor cells (as recited in instant claim 54).

Power and Hudson teach proteins on the surface of tumor cells that are targets for antibody therapy (see entire reference).

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It would have been *prima facie* obvious to one of ordinary skill in the art to generate a VHH antibody fragment such as taught by Lauwereys *et al* having specificity for a tumor target protein such as taught by Power and Hudson, and to have included it in a composition.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a composition for tumor therapy.

Furthermore, Power and Hudson teach designing these antibodies with radionuclides, toxins, enzymes, and drugs for clinical diagnosis and therapy. A radionuclide is a radioisotope, said radioisotope is another limitation of instant claim 35 (especially abstract and conclusion).

It would have been *prima facie* obvious to one of ordinary skill in the art to make an immunoconjugate such as taught by Power and Hudson using the antibody composition of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a composition for diagnosis and therapy, including for imaging.

20. Claims 19, 22 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frenken *et al* (J. of Biotechnology, 2000, 78: 11-21, of record) or Lauwereys *et al* (The EMBO Journal, 1998, 17(13): 3512-3520, of record) in view of Vaughn *et al* (Nature Biotechnology, 1998, 16: 535-539).

Frenken *et al* or Lauwereys *et al* have been discussed *supra*.

Frenken *et al* or Lauwereys *et al* do not teach a polypeptide comprising a variable region of a heavy polypeptide chain of an immunoglobulin that specifically binds an antigen of interest, said variable region itself containing an antigen binding site without contribution of a variable region of a light chain which is absent, wherein the said variable region is recombinantly fused to all or part of a constant region of a human antibody.

Vaughn *et al* teach that in order to improve therapeutic potential of antibodies that are recognized by humans as foreign, chimeric antibodies have been constructed in which the constant regions are replaced by their human counterparts. Vaughn *et al* teach recombinant technology for constructing chimeric and humanized antibodies (see entire reference, especially second full paragraph at column 2 on page 535).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have recombinantly fused the variable region taught by Frenken *et al* or Lauwereys *et al* to a human constant region such as taught by Vaughn *et al*.

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One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide for use in humans, the effector function of an immunoglobulin constant region well known to one of ordinary skill in the art at the time the invention was made, while avoiding potential immunogenicity of that region that is inherent in a non-human constant region, *i.e.*, in a constant region of the same species as the variable region of the antibody that the variable region is derived from.

21. Claims 18 and 25 appear to be free of the prior art.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
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October 30, 2009

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/Ram R. Shukla/

Supervisory Patent Examiner, Art Unit 1644